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EXAMINER BERTAGNA, ANGELA MARIE				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/566,223

**Applicant(s)**

TYAGI ET AL.

**Examiner**

ANGELA BERTAGNA

**Art Unit**

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 117-120 and 124-132 is/are pending in the application.
- 4a) Of the above claim(s) 130-132 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 117-120 and 124-129 is/are rejected.
- 7) ☒ Claim(s) 117, 118 and 127-129 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(c), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(c) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 3, 2009 has been entered.

Claims 117-120 and 124-132 are currently pending. In the response, Applicant amended claims 117, 118, and 124. Claims 130-132 remain withdrawn from consideration as being drawn to a non-elected invention.

The following include new grounds of rejection. Applicant's amendments to the claims have overcome the previously made objections to claims 117-118, and therefore, they have been withdrawn. Applicant's arguments filed on February 3, 2009 that remain pertinent to the new grounds of rejection have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section.

### ***Claim Objections***

2. Claim 117 is objected to because of the following informalities: In step (c), it would appear that "homogenizing the mixture" was intended for "homogenizing the mixing". Also, deleting the comma appearing after the word "DNA" in the last line of the claim is suggested.

Claim 118 is objected to because of the following informalities: This claim appears to be missing words, such as "occurs" or "is conducted", after the word "homogenizing" in line 2.

Claim 127 is objected to because of the following informalities: Deleting the comma appearing after the word "devRf3" is suggested. Also, adding a comma after the word "devRr3" and inserting the word "the" before the words "gene" and "microbe" is suggested.

Claim 128 is objected to because of the following informalities: Inserting the word "the" before the words "gene" and "microbe" in lines 2-3 is suggested.

Claim 129 is objected to because of the following informalities: Deleting the comma appearing after the word "devRf3" in line 2 is suggested. Inserting the word "the" before the words "gene" and "microbe" in line 3 is also suggested.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 117-120 and 124-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "effective", "economical", "simple", "safe", "rapid", and "sensitive" in independent claim 117 and the term "simple" in claim 124 are relative terms that render claim 117 and dependent claims 118-120 and 124-129 indefinite. The terms "effective", "economical", "simple", "safe", "rapid", and "sensitive" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is also noted that the above terms are

subjective terms whose scope depends entirely on the unrestrained opinion of the person practicing the method. As noted in MPEP 2173.05(b), "[T]he meaning of a term cannot depend on the unrestrained, subjective opinion of the person practicing the invention" citing *Datamize LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347-48, 75 USPQ2d 1801, 1807 (Fed. Cir. 2005). Accordingly, claims 117-120 and 124-129 are vague and indefinite.

Further regarding claims 117-120 and 124-129, the use of the exemplary phrases "such as", "including", and "like" in lines 3-4 of independent claim 117 renders the methods of claims 117-120 and 124-129 indefinite, because it is unclear whether the limitations following the phrases (*i.e.* tuberculosis and other mycobacterial infections caused by mycobacteria including *M. tuberculosis* and other infections caused by Gram-positive organisms like *Staphylococcus sp.*) are part of the claimed invention. See MPEP § 2173.05(d).

Claims 117-120 and 124-129 are further indefinite, because it cannot be determined from the language set forth in step (e) of independent claim 117 when washing the pellet obtained in step (d) is required. Claim 117 recites in step (e) that the pellet obtained in step (d) of the method is washed with solution 1 "optionally depending upon the decrease of the pellet size". Neither this language nor the specification makes clear what range of pellet sizes require washing with solution 1. Since the metes and bounds of independent claim 117 are unclear, claims 117-120 and 124-129 are indefinite.

Claims 117-120 and 124-129 are further indefinite, because it is unclear what is intended by the recitation "the processed sample being used in the form of smear, culture, or Polymerase chain reaction (PCR) starting material, using PCR amplifiable mycobacterial DNA, and RNA." It is unclear whether the above recitation is intended to require that the clinical sample processed

in the preceding steps is selected from a smear sample, a culture sample, or a sample containing PCR starting material (*i.e.* nucleic acids), or if the sample obtained at the conclusion of the method recited in claim 117 must be used in a PCR method, a smear microscopy method, or a culture method. It is also unclear whether the phrase "using PCR amplifiable mycobacterial DNA and RNA" refers only to the "PCR starting material" or if this phrase also requires the smear and culture sample to possess PCR amplifiable DNA and RNA.

Claim 125 is further indefinite, because it is unclear what is intended by the recitation "wherein said method in culture runs at a neutral pH". It is unclear whether the claim requires that when culture samples are used as the clinical sample processed by the method of claim 117, that the method of processing set forth in steps (a) - (g) of claim 117 occurs at a neutral pH, if only certain steps of the method of claim 117 must occur at a neutral pH, or if the sample obtained at the conclusion of the method recited in claim 117 is used in a culture method, which must be conducted at a neutral pH.

Claim 127 is further indefinite, because it appears to be incomplete, omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: amplifying a sample by PCR. Claim 127 is drawn to the method of claim 117 and defines the properties of primers used in a PCR amplification step. However, it is not clear from the language in claim 117 that PCR amplification is conducted either with the sample obtained at the conclusion of step (g) of the method or with another sample. Accordingly, the method of claim 127, which defines the properties of primers used in a PCR amplification process, appears to be missing essential method steps linking it to the method of claim 117.

Claims 128 and 129 are further indefinite, because they recite the limitation "the primers" in line 2. There is insufficient antecedent basis for this limitation in the claims.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 117-120 and 124-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of Herrmstadt et al. (US 6,027,883; newly cited).

These claims are drawn to a method for processing clinical samples using a composition comprising three solutions.

Regarding claim 117, Chakravorty teaches a method comprising:

- (a) obtaining a clinical sample (page 114, section 2.1)
- (b) mixing 1.5 – 2 volumes of a first solution with the sample and homogenizing the sample (see page 114, section 2.2.1, where solution 1 of Chakravorty comprises: 5 M GITC, 50 mM Tris-Cl, pH 7.5, 25 mM EDTA, 0.5% Sarcosyl, and 0.2 M  $\beta$ -mercaptoethanol)
- (c) adding a second solution to the homogenate and centrifuging to obtain a pellet (section 2.2.1 on page 114, where solution 1 of Chakravorty inherently includes water)
- (d) washing the pellet obtained in step (c) with the first solution (page 114, section 2.2.2)
- (e) washing the pellet of step (d) with water (page 114, section 2.2.2)
- (f) resuspending the water-washed pellet in solution A (*i.e.* a 10% suspension of a chelating resin), solution B (*i.e.* a 0.03% polyoxyethylene phenyl ethersolution), and solution C (*i.e.* a 0.3% solution of polysorbate 20) (page 114, section 2.2.3).

Chakravorty further teaches that the resulting solution is used for PCR amplification of mycobacterial DNA (page 114).

Regarding claim 118, Chakravorty teaches homogenization for 30-60 seconds (page 114, column 1).

Regarding claim 119, Chakravorty teaches that the above process can be performed in approximately three hours (page 116, column 2).

Regarding claim 120, the 5 M concentration of GITC is about 4 M, about 5 M, and about 6 M, and the 0.2 M concentration of  $\beta$ -mercaptoethanol is about 0.1 M or about 0.2 M. This concentration of  $\beta$ -mercaptoethanol is also within the claimed range of 0.1-0.2 M. It is further noted that the intended use recitations “for processing samples for culture and smear”, “for

processing of samples for culture, smear, and PCR”, and “samples processed for smear and PCR” have not been accorded patentable weight since they are intended use recitations (see MPEP 2111.02 II).

Regarding claim 124, Chakravorty teaches obtaining PCR-amplifiable DNA by adding 0.03% Triton X-100, which is within the claimed range of 0.01 - 0.1% (page 115, column 1). RNA is also inherently purified in the method of Chakravorty.

Regarding claim 125, the method of Chakravorty is performed at pH 7.5 (page 114).

Regarding claim 126, the samples used by Chakravorty were inherently stored at about -20°C for a time up to two months. It is also inherent that the samples can be processed for PCR, smear microscopy, and culture.

Chakravorty teaches the use of 5 M GITC in the first solution rather than 4-6 M GuHCl as required by claim 117. Also, Chakravorty does not explicitly state that the water used to prepare Solution 1 is sterile water. Chakravorty also teaches that the above sample processing method can be performed in approximately three hours (page 116, column 2) rather than the 1-2 hours required by claim 119. Regarding claim 124, Chakravorty teaches lysis in the presence of 0.03% Triton X-100, but does not teach that this embodiment of the method is performed in the absence of Solutions A, B, and C. Finally, regarding claim 125, Chakravorty teaches performing the method at a slightly alkaline pH of 7.5 rather than at neutral pH.

Jaber teaches a method for isolating DNA from *Mycobacterium tuberculosis* (pages 578-579). The method of Jaber comprises the following steps: (1) cell lysis in 6 M GuHCl, 50 mM EDTA, 1 mM 2-mercaptoethanol, 0.05% Tween 80; (2) ethanol precipitation, (3) washing with

lysis buffer, (4) phenol-chloroform and chloroform-isoamyl alcohol extraction, and (5) ethanol precipitation (see page 579).

Regarding claim 117, Jaber teaches that the chaotropic agent guanidinium hydrochloride, (GuHCl), “inactivates DNase and RNase, dissociates nucleoprotein, and disturbs cellular and subcellular structure, and its pH and ionic strength favor the native form of DNA (page 579, column 2).”

Herrnstadt teaches methods of isolating nucleic acids (see abstract and column 1, lines 50-61). Regarding claims 117-120 and 124-126, Herrnstadt teaches that guanidine hydrochloride and guanidine isothiocyanate are chaotropic agents suitable for disrupting tissue samples for subsequent DNA or RNA isolation (column 1, lines 35-40).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute GuHCl for GITC in the sample processing method taught by Chakravorty. An ordinary artisan would have been motivated to do so, because as evidenced by the teachings of Jaber (see pages 579-580) and Herrnstadt (see column 1, lines 35-40), GuHCl and GITC were known in the art at the time of invention to be equivalents useful for the same purpose, namely cell lysis. As noted in MPEP 2144.06, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. An ordinary artisan also would have been motivated to perform the method of Chakravorty using Triton X-100 in the absence of solutions A, B, and C, because Chakravorty taught that this detergent resulted in the best lysis and highest level of inhibitor removal (page 115) and that the Chelex-100 adsorption step (*i.e.* solution A treatment) only served to remove residual inhibitors that would not be present in samples with a low level of contaminants (page 116). An ordinary

artisan would have been motivated to eliminate unnecessary processing steps, such as treatment with solutions A, B, and C, because Chakravorty taught that multi-step processes resulted in sample loss and presented more contamination opportunities (page 116).

Regarding claims 118, 119, and 125, an ordinary artisan would have been motivated to optimize the homogenization time, the total processing time, and the pH at which the method was conducted in order to achieve the desired results. For example, an ordinary artisan would have been motivated to optimize the homogenization time in order to obtain maximal lysis without damaging the DNA. An ordinary artisan also would have been motivated to minimize the time required for performance of the method in order to increase efficiency. Moreover, as noted in MPEP 2144.05, “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).” Routine optimization is not inventive and no evidence has been presented to suggest that the selection of the claimed homogenization times, processing times, or pH values was other than routine or that the results should be considered to be unexpected compared to the prior art.

Finally, regarding step (d) in the method of claim 117, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to prepare the solution used by Chakravorty to dilute the homogenate using sterile water. An ordinary artisan would have recognized that doing so would have improved the method by reducing the likelihood of contamination stemming from the presence of microorganisms in the water used to prepare the solutions. It is also noted that dilution of the homogenate performed in step (d) of the method by adding sterile water constitutes an alteration of the concentration of the components of solution 1

used to prepare the homogenate. As noted in MPEP 2144.05 and as discussed above, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." In this case, no evidence has been presented to suggest that the claimed concentrations (*i.e.* those concentrations resulting from dilution of the homogenate with sterile water) are critical, and therefore, the methods of claims 117-120 and 124-126 are *prima facie* obvious over the cited references in the absence of secondary considerations.

6. Claims 127-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of Hermstadt et al. (US 6,027,883; newly cited) and further in view of GenBank Accession No. U22037 (March 1999; cited previously) and further in view of Marchetti et al. (Journal of Clinical Microbiology (1998) 36(6): 1512-1517; cited previously) and further in view of Buck et al. BioTechniques (1999) 27(3): 528-536; cited previously).

The combined teachings of Chakravorty, Jaber, and Hermstadt result in the method of claims 117-120 and 124-126, as discussed above.

Regarding claims 127-129, Chakravorty teaches using a set of primers designed from the *Mycobacterium tuberculosis* devR gene to amplify DNA isolated using the above method (page 114, column 2). However, Chakravorty does not teach amplification using two sets of primers,

wherein each primer set targets the devR gene and produces amplification products of 308 bp and 164 bp.

GenBank Accession No. U22037 teaches the complete nucleotide sequence of the *Mycobacterium tuberculosis* devR gene. The primers taught by Chakravorty are contained in this sequence and produce a 513 bp amplification product.

Marchetti teaches methods for amplifying *Mycobacterium tuberculosis* DNA by PCR (see abstract and page 1513). Marchetti compared the sensitivity of four different PCR primer pairs and determined that the use of primers designed to amplify shorter targets resulted in more sensitive detection than primers designed to amplify longer targets (see abstract and pages 1514-1515). Marchetti further stated, "PCR3 and PCR4, whose final amplification products are 106 and 123 bp long, respectively, showed the best results in terms of sensitivity compared to those of PCR1 and PCR2, which amplify longer fragments (223 and 143 bp, respectively). This suggests the need to choose the correct primers, with those amplifying relatively shorter DNA sequences, which are thus less prone to fragmentation, being favored (page 1515, column 2)."

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer

functioned as well (see page 533, column 1). Buck expressly states “The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize any set of primer pairs designed from the known *Mycobacterium tuberculosis* devR gene to amplify DNA isolated by the method resulting from the combined teachings of Chakravorty and Jaber. Since Marchetti taught that the use of primers designed to amplify short targets in the *Mycobacterium tuberculosis* genome resulted in increased sensitivity (pages 1514-1515), an ordinary artisan would have been motivated to design primer pairs targeting sequences shorter than the 513 bp region targeted by Chakravorty. An ordinary artisan would have had a reasonable expectation of success designing these primers since the complete devR gene sequence was known in the art at the time of invention as evidenced by GenBank Accession No. U22037. An ordinary artisan also would have had a reasonable expectation of success in using the primers in the method resulting from the combined teachings of Chakravorty and Jaber, since Buck demonstrated that essentially all primers were capable of an equivalent degree of extension when hybridized to a complementary target. Therefore, absent any secondary considerations, the

claimed methods are *prima facie* obvious in view of the combined teachings of Chakravorty, Jaber, Herrnstadt, Marchetti, GenBank Accession No. U22037, and Buck.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. \_\_\_, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at \_\_\_, 82 USPQ2d at 1397).”

In the instant case, as discussed above, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty and Jaber. The complete nucleotide sequence of the *Mycobacterium tuberculosis* gene disclosed in GenBank Accession No. U22037 presented the ordinary artisan with a finite number of possible primers for amplification. Then, since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by applying the teachings of Marchetti to the devR gene targeted by Chakravorty. Therefore, the methods of claims 127-129 are *prima facie* obvious over the cited references in the absence of secondary considerations.

***Response to Arguments***

7. Applicant's arguments filed on February 3, 2009 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 117-120 and 124-126 under 35 U.S.C. 103(a) as being unpatentable over Chakravorty in view of Jaber, Applicant first argues that Chakravorty does teach or suggest adding solution 2, which is a solution consisting of sterile water or 65-70 mM sodium phosphate at pH 6.7-6.8, to the homogenate in a separate step as required by independent claim 117 (pages 8-9). This argument was not persuasive, because the claims do not limit solution 2 to a solution consisting of sterile water or 65-70 mM sodium phosphate at pH 6.7-6.8, but rather a solution comprising sterile water or 65-70 mM sodium phosphate at pH 6.7-6.8. As discussed above, if the IRS solution utilized by Chakravorty to dilute the homogenate was not prepared using sterile water, it would have been obvious for the ordinary artisan to prepare this solution using sterile water, recognizing that doing so would eliminate a possible source of contamination. Also, as discussed above, adding sterile water to dilute the homogenate prior to centrifugation constitutes changing the concentration of the components of the solution used to prepare the homogenate. As noted in MPEP 2144.05, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." In this case, as discussed above, no evidence has been presented to suggest that reducing the concentration is critical, and therefore, the claimed concentrations are *prima facie* obvious in the absence of unexpected results.

Applicant also argues that Jaber teaches using GuHCl to lyse mycobacteria rather than tissue samples (page 8 and page 10-11). Applicant argues that the requirements for lysing tissue samples are more stringent than the requirements for lysing bacterial cells, and therefore, an ordinary artisan would not have had a reasonable expectation of success in substituting GuHCl for GITC. This argument was not persuasive, because as discussed above, the teachings of Herrnstadt indicate that GuHCl and GITC were art-recognized equivalents known to be useful for tissue disruption in methods of nucleic acid isolation (column 1, lines 35-40). Based on these teachings of Herrnstadt, an ordinary artisan would have had a reasonable expectation of success in using the IRS solution of Chakravorty containing GuHCl instead of GITC to practice the disclosed methods. Finally, it is noted that the clinical samples recited in the instant claims are not limited to tissue samples as argued by Applicant. The claims as written only require a clinical sample, which encompasses samples that are not tissue samples (*e.g.* bodily fluid samples or culture samples). As a result, Applicant's arguments regarding a reasonable expectation of success are not commensurate in scope with the claimed methods.

Applicant further argues that there is no motivation to combine the teachings of the cited references, since the method of Chakravorty utilizes centrifugation to isolate the DNA sample, whereas the method of Jaber utilizes precipitation to isolate DNA (pages 11-12). Applicant argues that the ethanol precipitation step is taught by Jaber to be critical, and therefore, an ordinary artisan would not reasonably expect a method wherein centrifugation is substituted by precipitation to produce PCR amplifiable DNA as required by the claimed methods (pages 11-12). Applicant further argues that these differences in the procedures of Chakravorty and Jaber do not suggest substituting GITC with GuHCl as stated in the rejection (pages 11-12). This

argument was not persuasive, because as discussed above, an ordinary artisan would have been motivated to substitute known art-recognized equivalents, such as GuHCl and GITC, when preparing the buffers used in the method of Chakravorty. As discussed previously, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results (MPEP 2144.06). Also, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Finally, Applicant argues that there is no motivation for the ordinary artisan to substitute GuHCl as taught by Jaber for GITC as taught by Chakravorty as stated in the rejection rather than simply substituting one lysis buffer for the other (pages 8 and 12). Applicant argues that the teachings of the cited references must be considered as a whole and that neither Jaber nor Chakravorty teaches that any of the components can be substituted with other components or altered (pages 12-13). In response to this argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed above, an ordinary artisan would have been motivated to substitute known art-recognized equivalents, such as GuHCl and GITC, when preparing the buffers used in the method of Chakravorty. As discussed

previously, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results (MPEP 2144.06). Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Regarding the rejection of claims 127-129 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Chakravorty, Jaber, GenBank Accession No. U22037, Marchetti, and Buck, Applicant first argues that independent claim 117 is allowable over Chakravorty and Jaber and that the additional cited secondary references do not overcome the deficiencies present in the primary combination of references (page 13). This argument was not persuasive, because as discussed above, the combined teachings of Chakravorty, Jaber, and Herrnsstadt render obvious the methods of claims 117-120 and 124-126.

Applicant also argues that there is no motivation to combine the cited references and select the claimed primers from the large number of primers suggested by the prior art (page 13). This argument was not persuasive, because as discussed previously, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty and Jaber. Application of the teachings of Marchetti to the method resulting from the combined teachings of Chakravorty and Jaber would result in the design of primer pairs (*e.g.* the claimed primer pairs) that produce shorter amplified products.

Also, in the recent decision *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.\_\_\_\_, 127 S. Ct. 1727 (2007)), the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the

fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at \_\_\_\_, 82 USPQ2d at 1397).

In this case, the complete nucleotide sequence of the *Mycobacterium tuberculosis* gene was disclosed in the prior art of GenBank Accession No. U22037 and presented the ordinary artisan with a finite number of possible primers for amplification. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by applying the teachings of Marchetti to the devR gene targeted by Chakravorty. The *KSR* decision makes clear that an explicit teaching, suggestion, or motivation is not required for a *prima facie* case of obviousness when an ordinary artisan would have combined known elements according to known procedures with predictable results (see MPEP 2141). In this case, the complete nucleic acid sequence of the devR gene was known in the art as evidenced by GenBank Accession Number U22037. Also, methods of primer synthesis and design were known in the art and were predictable as evidenced by the teachings of Chakravorty, Buck, and Marchetti. Thus, an ordinary artisan would have designed the claimed primers using the known devR sequence and known oligonucleotide synthesis methods and would have expected predictable results in doing so. Thus, in the absence of secondary considerations, the claimed primers are *prima facie* obvious over the cited references. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

***Conclusion***

8. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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amb

/Cynthia B. Wilder/  
Examiner, Art Unit 1637